

DOCKET NO.: ISIS-4824**PATENT****REMARKS**

Claims 28-39 are pending in the current case. Claim 40 has been added. Support for claim 40 can be found throughout the specification, specifically in paragraph 0017. No new matter has been added. The Applicants submit that in view of the following comments that the case is in proper form for allowance.

The Examiner has rejected claims 30-39 under 35 U.S.C. 103(a) as being unpatentable over WO99/60012 (Teng) in view of 5,672,359 (Digenis) and further in view of Muranishi. The Examiner states that Teng teaches a number of aspects of the instant invention. The Examiner further states that Teng does not explicitly teach that the drug is comprised in a first population of carrier particles with a bioadhesive and that the penetration enhancer is comprised in a second population of carrier particles wherein the first and second population are comprised in a single dosage form wherein the penetration enhancer activates the intestinal epithelium prior to arrival of the drug. The Examiner states that these deficiencies in the teachings of Teng are overcome by the teachings of Digenis.

The Examiner states that Digenis teaches a capsule made from starch, gelatin or a hydrophilic polymer such as HPMC which by virtue of its design and composition provides an immediate and sustained mode of release of its pharmacologically active or otherwise desirable components.

The Applicants submit that the multilayer capsule taught by Digenis is clearly distinct from the instant invention that teaches a first and second carrier particle composition wherein the first population comprises a drug-bioadhesive and the second population comprises a penetration enhancer. In paragraph 0016 of the specification it states that "By formulating the drug with a bioadhesive compound, the drug will acquire some degree of adhesive properties which will extend residence time and, consequently, absorptive properties, over the region of the intestine made permeable by the penetration enhancer." The combination of the drug with the bioadhesive into carrier particles, rather than with the penetration enhancer with the bioadhesive, or as a homogeneous mixture, is an essential aspect of the instant invention. The instant invention allows for the tissue to be activated by the penetration enhancer prior to the arrival of the drug as it transits through a maximum area of activated tissue. This arrangement

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of components is clearly stated in the claims which require the combination of drug and bioadhesive in a population of particles. Moreover, having two separate populations of particles allows for the preparation of an oral dosage formulation "in a manner that does not impair the adhesive or release properties of the other" population of particles as discussed in paragraph 0017.

This is clearly distinct from Digenis who teaches a "a hard capsule 10 which is formed from gelatin, starch, or hydrophilic polymer, and which comprises a three compartment delivery system for its pharmacologically active components" (col 9, lines 49-52). The hydrophilic polymer may be hydroxypropyl methylcellulose. As the hydroxypropyl methylcellulose forms the hard outer capsule, it cannot be formed into particles or commingled with the drug as claimed in claim 30. Therefore, claim 30 cannot be obvious in view of the combination of Teng and Digenis. As the remaining claims are dependent either directly or indirectly on claim 30, they are also not obvious in view of the cited references. Therefore the rejection for obviousness over 35 USC 103(a) is overcome.

The newly added claim 41 further states that the populations of carrier particles are released concurrently. This does not further limit the composition of the particles beyond what is claimed, only that the timing of their release from the formulation. As the claim includes all of the limitations of the allowable claim 30, it is also allowable.

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The Commissioner is hereby authorized to charge \$60.00 to Deposit Account 50-0252 referencing case number ISIS-4824 for a one month extension in time of response, small entity. It is believed that no further fee is due. However, if an additional fee is due, the Commissioner is hereby entitled to charge the Deposit Account listed above referencing this case.